HEPARIN—BOOTS

HEPARIN, a sodium salt of a mucoitin polysulphuric acid, first discovered by Howell and McLean in 1916, is the granular substance present in the mast cells which are distributed in the walls of the vascular and reticulo-endothelial systems; it is the normal physiological anticoagulant of the human blood. A detailed account of the chemistry and mode of action of heparin will be found in the work of Jorpes (*Heparin in the Treatment of Thrombosis*, London, 1946) to whom we owe much of our knowledge of the subject.

Heparin is the ideal anticoagulant; experimental work on rabbits has shown that these animals can tolerate, without any serious effects, repeated doses far in excess of those normally used clinically. This is in marked contrast to many of the synthetic anticoagulants, large doses of which tend to cause severe internal hæmorrhage. Heparin is heat-stable, is not readily destroyed by natural enzymes or chemicals, and is virtually free from toxic effects. The effects of overdosage can be readily neutralized by Injection of Protamine Sulphate.

STANDARDIZATION

Heparin—Boots is standardized, in our own Pharmacological Laboratories, in terms of International Units, one I.U. being the specific activity possessed by 0·0077 mg. of the Standard Preparation at present in use. Before issue, Heparin—Boots is required to pass a strict test for freedom from pyrogens.

Heparin—Boots and Injection of Protamine Sulphate—Boots are available in the following forms:—

Injection of Heparin, B.P.—Boots

A sterile solution in Normal Saline Solution containing 1,000, 5,000, or 25,000 I.U. per ml. in 5 ml. rubber-capped vials.

Injection of Heparin Retard—Boots

A sterile preparation containing 20,000 I.U. of Heparin, B.P. in 2 ml. in a modified Pitkin's menstruum.

Injection of Protamine Sulphate—Boots

A sterile solution containing 0·1 G. of protamine (salmine) sulphate in 10 ml.

INJECTION OF HEPARIN, B.P. —BOOTS—

Injection of Heparin, B.P.—Boots is a sterile solution of Heparin in Normal Saline Solution. It is pyrogen free, and the *p*H is adjusted to between 7·0 and 8·5.

INDICATIONS

Injection of Heparin, B.P. is indicated:—

(*a*) As a therapeutic agent in the treatment of:—

Phlebothrombosis.

Thrombophlebitis.

Pulmonary embolism.

Peripheral vascular disease, immersion foot, frost-bite, or local trauma associated with thrombosis and incipient gangrene.

(*b*) As a prophylactic measure in the prevention of phlebothrombosis in post-operative surgical cases, in gynæcology, and in congestive heart failure.

(*c*) As an anticoagulant in blood transfusion.

(*d*) As an adjuvant:—

To penicillin in the treatment of subacute bacterial endocarditis.

To dicoumarol in anticoagulant therapy.

Unlike dicoumarol, heparin is prompt in action and, besides being non-cumulative, entails no danger of over-prolonged action; over-dosage and side-effects from heparin are, therefore, controlled with relative ease.

Other uses of heparin

Apart from its use in the prevention and treatment of thrombo-embolic disease, heparin has been used with success in:—

Vascular surgery.

Vascular injury.

Post-traumatic gangrene.

Blood transfusion work in the new-born.

Pneumonia and other inflammatory conditions.

CONTRA-INDICATIONS

The use of Injection of Heparin, B.P. is contra-indicated in the following conditions:—

Active bleeding	Increased capillary fragility
Purpura	Intracranial hæmorrhage
Hæmorrhagic disorders	Intracranial vascular lesions
Presence of large, open wounds	Severe liver damage.

Heparin should not be administered during the first week of the puerperium, and should be used with caution in the presence of gastric or intestinal ulceration with bleeding.

METHOD OF ADMINISTRATION

Injection of Heparin, 1,000 or 5,000 I.U. per ml., is administered either by intermittent intravenous injection or by continuous intravenous drip.

Injection of Heparin, 25,000 I.U. per ml., is administered only by intramuscular injection. It should not be administered intravenously, undiluted.

DOSAGE

Intermittent intravenous injection

The usual initial dose is 10,000 to 15,000 I.U. of heparin, followed by doses of up to 10,000 I.U. given three to six times daily. These are continued until the required coagulation time is attained. Maintenance doses of up to 10,000 I.U. may then be given twice daily.

Continuous intravenous drip

By this method the hourly rate of administration is 1,000 to 2,000 I.U. in 100 ml. of Normal Saline Solution. The rate of flow is usually between 25 and 30 drops per minute.

Heparin therapy is generally maintained for a period of seven to ten days.

THE PATIENT SHOULD BE AMBULANT AS EARLY AS POSSIBLE DURING THE COURSE OF THERAPY.

PRECAUTIONS

Heparin should be used only when there are adequate facilities for determining blood coagulation times. Injection of Protamine Sulphate and matched whole blood for transfusion should be available.

The patient's hæmoglobin level should be checked frequently, since a fall may indicate a greater degree of local bleeding than is clinically apparent. Hæmaturia is also indicative of heparin overdosage.

The effects of overdosage can be readily neutralized by Injection of Protamine Sulphate (*see page 7*).

After intramuscular administration of Injection of Heparin, 25,000 I.U. per ml., or Injection of Heparin Retard, a hæmatoma occasionally forms at the site of injection. Apparent resistance to these preparations may be due to pooling of heparin at the injection site, which may result in severe local hæmorrhage or massive release of heparin into the blood stream, with resultant sudden increase in the clotting time.

INJECTION OF HEPARIN RETARD —BOOTS—

INJECTION OF HEPARIN RETARD—BOOTS is a sterile perparation of Heparin, B.P. in a modified Pitkin's menstruum, for *intramuscular* or *deep subcutaneous* injection.

Each 2 ml. ampoule contains:—

Heparin, B.P.	20,000 I.U.
Gelatin, B.P.	18 per cent. w/v
Dextrose, B.P.	9 per cent. w/v
Acetic Acid, B.P.	1·5 per cent. v/v
Water for Injection, B.P.	to 100 per cent.

INDICATIONS

Injection of Heparin Retard—Boots exerts a prolonged anticoagulant action which obviates the necessity for repeated intravenous injections of heparin.

It can be used for the prophylaxis and treatment of all the thrombo-embolic conditions for which Injection of Heparin, B.P. is employed.

CONTRA-INDICATIONS

The contra-indications to the use of Injection of Heparin, B.P. (*see page 2*) also apply to the use of Injection of Heparin Retard.

METHOD OF ADMINISTRATION

The ampoule is gently warmed by holding it under a running hot water tap, or by immersing it in a container of hot water until the contents become fluid. It is then shaken, and the contents drawn into a dry, warm, sterile, 5 or 10 ml. syringe, using a sterile, gauge 18 needle, two inches in length.

A gauge 20 needle is substituted for the actual injection, which is performed immediately into the deep subcutaneous or superficial intramuscular tissue of the anterior or lateral aspect of the thigh. Subsequent injections are given into alternate thighs, the site of the previous injection being avoided. In patients with thrombophlebitis, the preparation is injected into the normal thigh, use of the affected thigh being avoided altogether if there is œdema.

The injection usually causes some pain, with swelling and tenderness of the tissues surrounding the injection site. These effects can be minimized by concomitant injection of a 2 per cent. solution of procaine hydrochloride.

The heparin effect can be delayed, if desired, by applying either an ice-bag to the depot area, or a tourniquet proximally to it.

DOSAGE

Since the response to heparin varies with the individual patient, a precise dosage schedule for Injection of Heparin Retard cannot be given.

The patient's clotting time should be determined before treatment.

The usual initial dose is 2 ml. (20,000 I.U.). Further injections are usually given at twelve-hourly intervals, *e.g.*, at noon and midnight, and estimations of clotting time performed at 4 p.m. and 10 a.m. If the clotting time is between fifteen and thirty minutes, the required dose is probably 20,000 I.U., but if the clotting time is below fifteen minutes, 40,000 I.U. may be necessary. If the clotting time has risen above thirty minutes, no further heparin is administered until it has again fallen below twenty-five minutes.

The clotting time is measured by Lee and White's method, in which the normal clotting time is between three and eight minutes. During heparinization with Injection of Heparin Retard the ideal is to control it at about twenty-five minutes.

PRECAUTIONS

INJECTION OF HEPARIN RETARD SHOULD NOT BE ADMINISTERED INTRAVENOUSLY.

The precautions to be taken when using Injection of Heparin, B.P. must also be observed when using Injection of Heparin Retard.

The effects of overdosage can readily be neutralized by Injection of Protamine Sulphate—Boots (*see page* 7).

INJECTION OF PROTAMINE SULPHATE —BOOTS—

INJECTION OF PROTAMINE SULPHATE—BOOTS is a sterile, 1 per cent. solution of protamine (salmine) sulphate, the *p*H being adjusted to between 2·5 and 3.

INDICATIONS

For restoring the original coagulation time of the blood during heparin treatment, *e.g.*, when heparin has been given during an operation on blood vessels or when hæmorrhage has unexpectedly occurred during heparin treatment.

METHOD OF ADMINISTRATION

Injection of Protamine Sulphate is injected slowly by the intravenous route, either alone, or diluted with Normal Saline.

DOSAGE

The anticoagulant effect produced by injecting 5,000 units of heparin is approximately neutralized by an injection of 50 mg. of protamine sulphate (5 ml. Injection of Protamine Sulphate) given fifteen minutes later. If a longer time has elapsed proportionately less protamine sulphate is required. The approximate amount of protamine sulphate required to produce an immediate return to the initial coagulation time can, therefore, be determined from the amount of heparin given over the previous three to four hours.

The effect produced by administration of Injection of Heparin Retard may be rapidly counteracted, irrespective of the dosage, by giving an intravenous injection of 10 ml. of Injection of Protamine Sulphate.

TOXICITY

Although the injection of large amounts of protamine sulphate produces toxic reactions in animals, no undesirable effects occur in man after slow intravenous administration of normal doses following heparin therapy.

INJECTION OF HEPARIN, B.P.—BOOTS

1,000, 5,000 or 25,000 per ml.
5 ml. rubber-capped vials.

INJECTION OF HEPARIN RETARD—BOOTS

2 ml. ampoules
each containing 20,000 I.U. of Heparin, B.P. in a modified Pitkin's menstruum.
Boxes of six ampoules.

INJECTION OF PROTAMINE SULPHATE—BOOTS

10 ml. ampoules
each containing 0·1 G. of protamine (salmine) sulphate.
Boxes of six ampoules.

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